## REMARKS

Reconsideration is respectfully requested. Claims 60-69 are pending. Claims 1-59 have been canceled.

With respect to all amendments and cancelled claims, Applicants have not dedicated or abandoned any unclaimed subject matter and moreover have not acquiesced to any rejections and/or objections made by the Patent Office. Applicants reserve the right to pursue prosecution of any presently excluded claim embodiments in future continuation and/or divisional applications.

## Claim Rejection Under 35 U.S.C. § 103

Claims 60-69 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Kayyem et al. (WO 98/20162) ("*Kayyem*"), in view of Shuber (US 5,633,134) ("*Shuber*"). Applicants respectfully traverse.

### 1) The *Graham* Factors

When rejecting claims under 35 U.S.C. §103, the Examiner bears the initial burden of factually supporting any *prima facie* conclusion of obviousness. MPEP §2142. The inquiry of obviousness is controlled by the *Grahm* factors. See *KSR International Co. v. Teleflex Inc.* 1727 S.C.t (2007) (citing *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1 (1966)). These factors are: 1) the scope and content of the prior art; 2) the differences between the prior art and the claims; 3) the level of ordinary skill in the pertinent art; and 4) objective evidence of nonobviousness.

(A) *Kayyem*

*Kayyem* is directed to methods of detecting a target sequence in a nucleic acid sample using a probe with electron transfer moieties. See page 36, lines 1-20.

(B) *Shuber*

*Shuber* is directed to the use of allele specific oligonucleotide (ASO) probes in the presence of a quaternary ammonium salt. In general, Shuber is concerned with testing large numbers of individuals for the presence or absence of multiple mutations in one or more genes. See Abstract.

Particularly, *Shuber* discloses a two-step method to detect multiple mutations in one or more genes simultaneously. In the first step, multiple probes are pooled together to hybridize with the sample DNA. If there is a positive result, in a second step, each individual probe is used to hybridize with the sample DNA separately to determine if any of the probes will hybridize to the sample DNA. In all cases where *Shuber* utilizes multiple probes in a single reaction, any positive result in the first reaction gives rise to the necessity of doing individual single probe reactions. That is, when multiple probes are used, there is no "determining the nucleotide" at a particular position; an individual reaction is required to determine which mutation is present.

For example, as outlined in column 6, line 67 on, in the development of a cystic fibrosis test, analysis of 12 mutations was broken down into four individual hybridizations. The first hybridization uses the probe with wide-type at position 508; the second hybridization uses the probe with delta F508 mutations; the third hybridization uses a pool of five probes; and the forth uses probes of the other six mutations. Col. 7, ll. 1-8. In a second round, "[p]ool-positive samples were subsequently hybridized *independently* with the relevant ASOs to identify the specific mutation or mutations involved." Col. 7, ll. 27-29 (emphasis added).

(C) *Shuber* does not teach "a second label probe ... comprising ... a second ETM with a second redox potential."

Claims 61-69 depend from claim 60, which requires "a first label probe ... comprising ... a first electron transfer moiety (ETM) with a first redox potential," and "a second label probe ... comprising ... a second ETM with a second redox potential." Thus the pending claims require at least two probes, each with a different label (i.e. ETM with different redox potentials) that could be used to distinguish which probe actually hybridizes to the target sequence.

In contrast, *Shuber* discloses using multiple probes with the same label, such as $^{32}P$. For example, *Shuber* discloses that "$^{32}P$-labeled mutation specific ASO probes [] were made from the ASO sequences shown [i]n Table." Col. 5, ll. 20-21. It does not teach probes with different labels. *Shuber* references other labels:

> ASOs can also be labeled by non-isotopic methods (e.g. via direct or indirect attachment of fluorochromes or enzymes, or by various chemical modifications of the nucleic acid fragments that render them detectable immunochemically or by other affinity reactions. Col. 3, ll. 7-12.

However, *Shuber* does not choose to use any of these labels, or to use more than one labels to label different probes.

*Shuber* further discloses pooling the different probes with the *same* $^{32}P$ label together for the hybridization with the sample DNA: "Hybridizations were carried out in plastic bags containing pooled $^{32}P$-labeled ASO probes shown in Table 1." Col. 5, ll. 39-40.

Under the *Shuber* method, the hybridization of any probe in the pool to the sample DNA would give rise to a positive signal. However, it would not reveal which probe(s) hybridize to the sample DNA because all the probes have the *same* label. As such, it is necessary for the *Shuber* method to conduct a second round of test with *each individual* probe to determine of the identity of a particular probe that hybridizes to the sample DNA in the first step. In fact, *Shuber* states:

The frequency of each mutation determined how often it was necessary to follow up a pool-positive result with *individual* ASO hybridization. Col. 6, ll. 9-12 (emphasis added).

Pool-positive samples were subsequently hybridized *independently* with the relevant ASOs to identify the specific mutation or mutations involved. Col. 7, ll. 27-29 (emphasis added).

As such, Shuber *discloses* using multiple probes with same label. It does not teach using multiple probes with different labels as required by the pending claims.

(D) *Schuber* does not teach using of multiple probes to interrogate the same detection position in a target sequence

The pending claims recite "a first detection position" in a target sequence and "determining the nucleotide(s) at said detection position." Thus the pending claims require using multiple probes to interrogate the same detection position in a target sequence. For example, one embodiment of the invention would be using two probes to determine the single nucleotide polymorphism (SNP) at the detection position.

In contrast, *Shuber* discloses using ASO probes "recognizing multiple regions on the same gene or multiple genes on the same or different chromosomes." Col. 2, ll. 20-24. It discloses:

[A] process for simultaneously detecting the presence or absence of multiple mutations (i.e. more than one mutation) in a DNA sample by hybridizing the sample with multiple allele specific oligonucleotide probes ... and detecting hybridization as an indication of the presence of at least one mutation in the sample." Col. 2, ll. 29-37.

As such, *Shuber* discloses using multiple probes to interrogate different positions. It does not teach the use of multiple probes to interrogate the same detection position in a target sequence as the pending claims require.

**2) There is no motivation to combine *Kayyem* with *Shuber* to reach the claimed invention.**

"[A] patent composed of several elements is not proved obviousness merely by demonstrating that each of its elements was, independently, known in the prior art.... [I]t can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does." *KSR*, at 1743.

*Shuber* teaches away from the claimed invention.

"[W]hen the prior art teaches away from combining certain known elements, discovery of a successful means of combining them is more likely to be nonobvious." KSR, at 1740. "[A] reference may teach away when a person skilled in the art, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant." *In re ICON Health and Fitness Inc.*, 83 USPQ2d 1746, 1751 (Fed. Cir. 2007).

As presented above, *Shuber* discloses a two-step process using multiple probes to detect multiple mutations with each probe having the same label. This is opposite to the use of multiple distinguishable probes in a single step. Thus, a skilled artisan, upon reading *Shuber*, would be led a in direction divergent from the path that was taken by the applicants, i.e. using multiple probes to detect the identity of nucleotide(s) in the same detection position, with each probe having different labels.

For the foreging reasons, the Examiner failed to establish a *prima facie* case of obviousness. The rejection is improper and should be withdrawn.

## CONCLUSION

Applicants respectfully submit that the claims are now in condition for allowance and early notification to that effect is respectfully requested. If the Examiner feels there are further unresolved issues, the Examiner is respectfully requested to phone the undersigned at (415) 442-1000.

Respectfully submitted,
MORGAN, LEWIS & BOCKIUS LLP

Dated: 10/31/2007 By: _____
Tao Huang, Ph.D., Reg. No. 60,008, for
Robin M. Silva, Reg. No. 38,304

*Filed Under 37 C.F.R. § 1.34*

**Customer No.: 67374**
MORGAN, LEWIS & BOCKIUS LLP
One Market, Spear Street Tower
San Francisco, CA 94105
Telephone: (415) 442-1000
Facsimile: (415) 442-1001